detail below, Applicants request that each of these objections and rejections be removed and that the claims be allowed to issue.

1. The Title Has Been Amended

The Examiner has objected to the title as not descriptive, and suggested a new title.

Applicants have amended the title according to the Examiner's suggestion, so that the rejection should be removed.

2. The Claims Are Not Indefinite

Claims 7, 9, 11, 13, 15, 17 and 20 are rejected under 35 U.S.C. §112 as indefinite in use of the term "natural," and has suggested that this rejection could be overcome by deleting the term "natural" from the claims.

Applicants have deleted the term "natural" from the claims, so that this rejection should be withdrawn.

3. The Rejection Under 35 U.S.C. §102 Is Obviated

Claim 20 is rejected under 35 U.S.C. §102(b) as anticipated by Cummins et al., International Patent Application Publication WO 88/03411 ("Cummins 1"). The Examiner states:

> Cummins et al. teaches a pharmaceutical agent, human alpha interferon, and its process of preparation (pg. 13-16). Cummins et al. also teaches that human [alpha]-interferon as a liquid formulation is administered through the peroral route at a daily dosage of 0.01 to about 5 IU per pound (pg. 27, 29-31; claim 1). Therefore, for typical patients weighing from about 100 to 225 pounds, the preferred dosages are thus on the order of 5-

1,125 IU [alpha]-interferon per day. Additionally, the recitation of "packaging material/label" in claim 20 fails to distinguish the claims from prior art because written material is not protected under patent law. Also, the written material is tantamount to an intended use, which is not given patentable weight.

In order to put the application in order for allowance, Applicants have cancelled claim 20, without prejudice, so that the rejection should be withdrawn.

4. The Claims Are Not Obvious

4.1 Claims 7, 11, 13 and 17

Claims 7, 11, 13 and 17 are rejected under 35 U.S.C. §103(a) as obvious over Di Bisceglie et al, 1989, New Engl. J. Med. 321:1506-1510 ("Di Bisceglie") in view of either of Cummins 1 or United States Patent No. 5,824,300 by Cummins ("Cummins 2").

The Examiner cites Di Bisceglie as teaching daily subcutaneous administration of human alpha-interferon to subjects having type C viral hepatitis, but acknowledges that Di Bisceglie does not teach administration of an oral liquid formulation of alpha-interferon at the dosages claimed.

The Examiner states that each of the Cummins references teaches liquid formulations of alpha-interferon administered in a dose range of from about 0.5 to 1.5 IU per pound per day, which, according to the Examiner's calculation, would result in preferred dosages of from about 50 to 340 IU per day. Subject matter of various other claim limitations, including leukocyte source, single or divided doses, and a dose volume of one tablespoon are also characterized as being disclosed by either or both Cummins references.

The Examiner concludes:

> It would have been obvious to one having ordinary skill in the art at the time the invention was made to prepare a liquid formulation containing 1-1500 IU of human leukocyte [alpha]-interferon in a convenient single-dose delivery volume for oral administration as taught by Cummins to treat a subject having type C viral hepatitis as taught by Di Bisceglie et al. The person of ordinary skill in the art would have been motivated to make that modification because oral delivery of [alpha]-interferon (contact with the oral and pharyngeal mucosa) would achieve better results as compared to other forms of delivery, such as intramuscularly or intradermally. The person of ordinary skill in the art would have expected success because human [alpha]-interferon was already being administered to subjects with type C viral hepatitis at the time the invention was made. . . . The concentration range claimed by applicant overlaps the prior art range, and the prior art and the claimed formulations comprise the same active ingredients and are employed in the same manner, *i.e.*, oral delivery in a manner that promotes contact between the liquid [alpha]-interferon solution and the oropharyngeal mucosae.

Applicants respectfully disagree, and assert that the claims are not obvious. Section 2142 of the Manual of Patent Examining Procedures states:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *in re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

The present rejection does not meet this standard, for the following reasons.

First, there is no motivation to combine the reference teachings to arrive at the claimed invention. Cummins 1 and 2 are general references relating to interferon use for the treatment of a wide variety of diseases which do not specifically include hepatitis C infection. As stated in Applicant's Request for Continued Examination, Cummins 1 and 2 focus on disorders primarily affecting the immune system:

> Interferon contacting the oral and/or pharyngeal mucosa, in amounts of less than 5 IU/lb of body weight per day is consistently effective to potentiate disease-corrective immune responses in vertebrates afflicted with immuno-resistant disease states characterized by apparent hyperactive or hypoactive immune system function. Treatment in accordance with the present invention has been shown to effect remission of neoplastic disease, hyperallergenicity, immuno-resistant or immuno-debilitating viral infections and autoimmune disorders characterized by chronic tissue degenerative inflammation .[1]

Cummins 1 and 2 additionally state that the disclosed methods may be used to treat human and animal infections, and provide examples of viruses which could be treated:

> Exemplary of human viral infections showing remarkable response to treatment in accordance with the present invention are infections of human rhinovirus (common cold), herpes simplex I virus (cold sores) and human papovavirus (warts). Based on treatment results to date, it is expected that contact of interferon at low dosage with the oral and pharyngeal mucosa will provide an effective treatment for Acquired Immune Deficiency Syndrome (AIDS) and disease conditions having the herpes simplex II virus as the causative agent. A patient experiencing a condition of viral myocarditis has responded favorably to the present treatment. Warts often dissipate within six to eight weeks after initiating treatment in accordance with this invention. Interferon administration in accordance with this invention can also be used to help prevent viral infections, for example, infections by the causative agents of flus and colds, and to minimize the symptoms associated with such viral infections.[2]

Hepatitis C is *not* mentioned. The foregoing text was published in Cummins 1 and therefore publicly available as of its publication date, May 19, 1988.

In contrast to the generality of the Cummins references, Di Bisceglie relates specifically to hepatitis C. Di Bisceglie is a report by clinicians of the National Institutes of Health and was published in the prestigious New England Journal of Medicine *after* Cummins 1. Di Bisceglie concludes:

> Interferon alfa given in a dose of 2 million units three times a week for six months reduced disease activity in chronic hepatitis C as assessed by serial testing of serum aminotransferase activities and liver-biopsy histology.

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[1] Cummins 1, page through page 6 line 7; Cummins 2, column 3 lines 12-22.
[2] Cummins 1, page 10 lines 14-27; Cummins 2, column 5 lines 12-29.

> However, the beneficial effect was transient in most patients. ***Further studies should focus on higher doses of interferon alfa given for longer periods***. (emphasis added)[1]

Therefore, not only is there no suggestion to combine the references, there is a teaching in Di Bisceglie, the more specific, later reference, *not* to use lower doses as taught by Cummins 1 and 2. Accordingly, these references should not be combined, and the rejection should be removed.

Second, even if the references were, for the sake of argument, combined, they convey no expectation of success. Cummins 1 and 2 are broad and general disclosures and do not mention treatment of hepatitis C. Di Bisceglie is specifically directed toward hepatitis C, teaches that "[t]here is currently no therapy of established benefit for chronic hepatitis C", and urges that doses of alpha-interferon *greater than 2 million units three times per week* might offer improved clinical results. This means that Di Bisceglie, based on its clinical data, in a paper published approximately 1.5 years after Cummins 1, is recommending that a weekly dosage of greater than 6 million units of interferon be used in clinical trials. The highest weekly dose literally covered by the claims is 3500 units - approximately 1700-fold less. Moreover, Di Bisceglie administered alpha-interferon subcutaneously Based on these facts, why would the skilled artisan reasonably expect the low oral dose claimed to be successful? Applicants also note that. since Cummins 1 was in the public domain 1.5 years before Di Bisceglie was published, given the presumed expertise of the scientists involved in the NIH clinical trial, they should be considered constructively aware of Cummins and yet did not recommend a lower dose.

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[1] Di Bisceglie, page 1510.

Furthermore, as evidence of the state of the art at the time the present invention was made, Applicants invite the Examiner's attention to the NIH Consensus Statement, 1997, March 24-26, 15(3):1-41, a copy of which is attached hereto as Exhibit A, having an abstract as follows:

> OBJECTIVE: To provide health care providers, patients, and the general public with a responsible assessment of current available methods to diagnose, treat, and manage hepatitis C. PARTICIPANTS: ***A non-Federal, nonadvocate, 12-member panel representing the fields of general internal medicine, hepatology, gastroenterology, infectious diseases, medical ethics, transfusion medicine, epidemiology, biostatistics, and the public. In addition, 25 experts from these same fields presented data to the panel and a conference audience of 1,600. EVIDENCE: The literature was searched through Medline and an extensive bibliography of references was provided to the panel and the conference audience. Experts prepared abstracts with relevant citations from the literature. Scientific evidence was given precedence over clinical anecdotal experience.*** CONSENSUS PROCESS: The panel members, answering predefined questions, developed their conclusions based on the scientific evidence presented in open forum and the scientific literature. The panel composed a draft statement that was read in its entirety and circulated to the experts and the audience for comment. Thereafter, the panel resolved conflicting recommendations and released a revised statement at the end of the conference. The panel finalized the revisions within a few weeks after the conference. CONCLUSIONS: Hepatitis C is a common infection with a variable course that can lead to chronic hepatitis, cirrhosis, and hepatocellular carcinoma. The course of illness may be adversely affected by various factors, especially alcohol consumption. Therefore, more than one drink per day is strongly discouraged in patients with hepatitis C, and abstinence from alcohol is recommended. ***Initial therapy with interferon alfa (or equivalent) should be 3 million units three times per week for 12 months. Patients not responding to therapy after 3 months should not receive further treatment with interferon alone, but should be considered for combination therapy of interferon and ribavirin or for enrollment in investigational studies.*** Individuals infected with the hepatitis C virus should not donate blood, organs, tissues, or semen. Safe sexual practices, including the use of latex condoms, is strongly encouraged for individuals with multiple sexual partners. Expansion of needle exchange programs should be considered in an effort to reduce the rate of transmission of hepatitis C among injection drug users. (emphasis added).

Thus, a formal review of the art by clinical authorities performed at approximately the time the instant invention was made[4] did not find it obvious to administer low-dose oral alpha-interferon for the treatment of hepatitis C, but rather recommended that a much higher subcutaneous dose be used (9 million units per week compared to the claimed weekly dosage of at most about 3500 units). Applicants assert that this demonstrates that the claimed subject matter is not obvious over the prior art.

Accordingly, it is requested that the rejection be withdrawn.

4.2 Claims 9 And 15

Claims 9 and 15 are rejected under 35 U.S.C. § 103(a) as obvious over Di Bisceglie and either Cummins 1 or 2 (as applied to claims 7, 11, 13 and 17) and further in view of Ratajczak et al., 1993, Arch. Immunol. Ther. Exp. 41:237-240 ("Ratajczak"), which, according to the Examiner, "describes the use of lozenges containing 50 or 100IU of human lymphobloastoid [alpha]-interferon for oropharyngeal delivery in the treatment of hepatitis B infections."

The Examiner concludes:

> It would have been obvious to one having ordinary skill in the art at the time the invention was made to prepare an aqueous formulation of human [alpha]-interferon according to Cummins [1 or 2], employing lymphoblastoid [alpha]-interferon as described by Ratajczak in place of the buffy coat leukocyte [alpha]-interferon noted particularly by Cummins, because Ratajczak evidences that lymphoblastoid interferon was readily available at the time of the invention and teaches that it is suitable for the treatment of exemplary viral disease *via* delivery to the oropharyngeal mucosae. It consequently would have been obvious to the artisan that lymphoblastoid interferon would be the functional equivalent of the human [alpha]-interferon liquid preparations expressly described by Cummins [1 or 2] for use in the treatment of subjects having type C viral

[4] The earliest priority date claimed for this application is based on Italian Patent Application RM96A000136, filed February 28, 1996.

hepatitis as described in Di Bisceglie et al. The claimed invention would have been *prima facie* obvious as a whole at the time it was made, especially in the absence of evidence to the contrary.

For the same reasons as set forth regarding the rejection of claims 7, 11, 13 and 17, Applicants assert that claims 9 and 15 are not obvious. The mere disclosure that alpha-interferon could be incorporated in a lozenge for treating a disease caused by a distinct viral agent (hepadnavirus (hepatitis B) rather than flavivirus-like (hepatitis C)) does not render obvious what the combination of Cummins 1 and 2 and Di Bisceglie cannot. Accordingly, Applicants request that this rejection be withdrawn.

5. Conclusion

For all the foregoing reasons, Applicants request that all rejections and objections be withdrawn and that the claims be allowed to issue.

Respectfully submitted,

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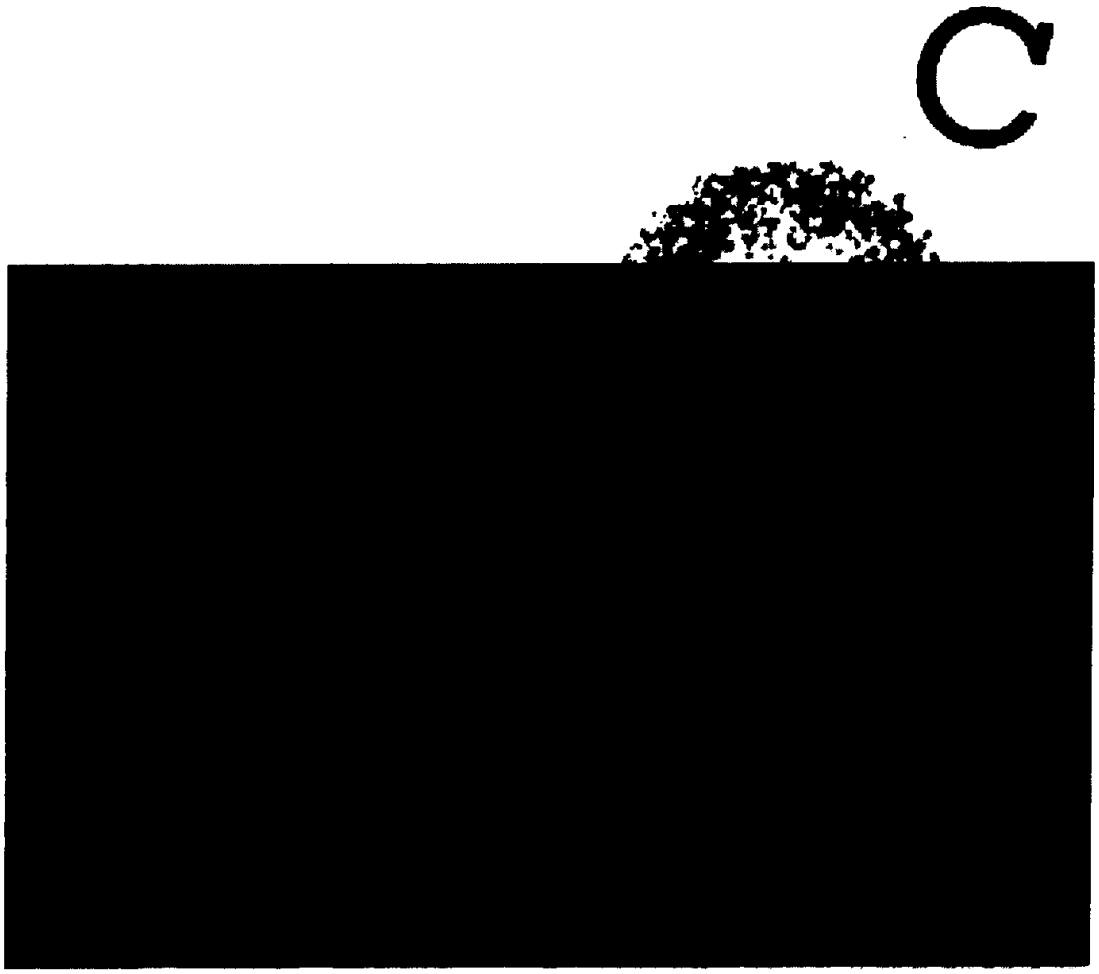
ATTORNEYS FOR APPLICANTS

CLAIM 7 MARKED TO SHOW REVISION

7. (three times amended) A method of treating a subject having type C viral hepatitis comprising administering, to the subject, by the peroral route, an oral liquid formulation of [natural] human α-interferon at a daily dosage of between 100 and 500 IU.

NIH Consensus Statement

Volume 15, Number 3
March 24-26, 1997



Management of Hepatitis C

NATIONAL INSTITUTES OF HEALTH
Office of the Director

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Reference Information

For making bibliographic reference to this consensus statement, it is recommended that the following format be used, with or without source abbreviations, but without authorship attribution:

Management of Hepatitis C. NIH Consens Statement 1997 Mar 24-26; 15(3): 1-41.

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NIH Consensus Statement
Volume 15, Number 3
March 24-26, 1997

Management of Hepatitis C

This statement reflects the panel's assessment of medical knowledge available at the time the statement was written. Thus, it provides a "snapshot in time" of the state of knowledge on the conference topic. When reading the statement, keep in mind that new knowledge is inevitably accumulating through medical research.

National Institutes Of Health
Continuing Medical Education

NATIONAL INSTITUTES OF HEALTH
Office of the Director

Abstract

Objective

To provide health care providers, patients, and the general public with a responsible assessment of current available methods to diagnose, treat, and manage hepatitis C.

Participants

A non-Federal, nonadvocate, 12-member panel representing the fields of general internal medicine, hepatology, gastroenterology, infectious diseases, medical ethics, transfusion medicine, epidemiology, biostatistics, and the public. In addition, 25 experts from these same fields presented data to the panel and a conference audience of 1,600.

Evidence

The literature was searched through Medline and an extensive bibliography of references was provided to the panel and the conference audience. Experts prepared abstracts with relevant citations from the literature. Scientific evidence was given precedence over clinical anecdotal experience.

Consensus Process

The panel members, answering predefined questions, developed their conclusions based on the scientific evidence presented in open forum and the scientific literature. The panel composed a draft statement that was read in its entirety and circulated to the experts and the audience for comment. Thereafter, the panel resolved conflicting recommendations and released a revised statement at the end of the conference. The panel finalized the revisions within a few weeks after the conference

Conclusions

Hepatitis C is a common infection with a variable course that can lead to chronic hepatitis, cirrhosis, and hepatocellular carcinoma. The course of illness may be adversely affected by various factors, especially alcohol consumption. Therefore, more than one drink per day is strongly discouraged in patients with hepatitis C, and abstinence from alcohol is recommended. Initial therapy with interferon alfa (or equivalent) should be 3 million units three times per week for 12 months. Patients not responding to therapy after 3 months should not receive further treatment with interferon alone, but should be considered for combination therapy of interferon and ribavirin or for enrollment in investigational studies. Individuals infected with the hepatitis C virus should not donate blood, organs, tissues, or semen. Safe sexual practices, including the use of latex condoms, is strongly encouraged for individuals with multiple sexual partners. Expansion of needle exchange programs should be considered in an effort to reduce the rate of transmission of hepatitis C among injection drug users.

Introduction

The hepatitis C virus (HCV) is one of six viruses (A, B, C, D, E, and G) that together account for the majority of cases of viral hepatitis. According to the National Health and Nutrition Examination Survey of 1988-94 and other population-based surveys, estimates of the incidence and prevalence of HCV infection have been made. Nearly 4 million Americans are infected with hepatitis C. The infection is more common in minority populations (3.2 percent of African-Americans and 2.1 percent of Mexican-Americans) than in non-Hispanic whites (1.5 percent). The incidence of hepatitis C infection appears to be declining since its peak in 1989. Currently, approximately 30,000 acute new infections are estimated to occur each year, about 25 to 30 percent of which are diagnosed. Hepatitis C accounts for 20 percent of all cases of acute hepatitis. Currently, hepatitis C is responsible for an estimated 8,000 to 10,000 deaths annually, and without effective intervention that number is postulated to triple in the next 10 to 20 years. Hepatitis C is now the leading reason for liver transplantation in the United States.

The switch from commercial to volunteer blood donors and the development of a diagnostic blood test for hepatitis B in the early 1970s led to screening of blood donors and reduced from 30 to 10 percent the incidence of hepatitis following multiple transfusions. The remainder of these transfusion-associated cases were termed "non-A, non-B" hepatitis. In 1989, Michael Houghton and his colleagues ushered in a new era for the discovery of infectious agents when they used molecular biologic techniques to clone hepatitis C, the agent responsible for 80 to 90 percent of non-A, non-B hepatitis. This was a scientific tour de force because the technique was successful in identifying an agent that had not been visualized, grown in culture, or immunologically defined. Following the introduction of sensitive and effective blood tests for the detection of hepatitis C, the risk of transfusion-related hepatitis is now in the range of 1 in 100,000 units transfused.

Hepatitis C is transmitted primarily by the parenteral route, and sources of infection include injection drug use, needlestick accidents, and transfusions of blood or blood products. Since 1990 and the introduction of tests for anti-HCV, new cases of posttransfusion hepatitis C have virtually disappeared. Hepatitis C virus is not easily cleared by the host's immunologic defenses. Thus, a persistent infection develops in perhaps as many as 85 percent of patients with acute hepatitis C. This inability to clear the virus by the infected host sets the stage for the development of chronic liver disease. The range of disease states following hepatitis C infection is broad. In contrast to hepatitis A and B, there is no effective vaccine to prevent acquisition of hepatitis C infection.

For the reasons listed above, the National Institute of Diabetes and Digestive and Kidney Diseases and the Office of Medical Applications of Research of the National Institutes of Health, along with cosponsors, the National Institute of Allergy and Infectious Diseases, National Heart, Lung, and Blood Institute, National Institute on Drug Abuse, and Centers for Disease Control and Prevention, sponsored a Consensus Development Conference on March 24-26, 1997. Following 1½ days of testimony by experts in the relevant fields and discussion from the audience, a consensus panel representing general internal medicine, hepatology, gastroenterology, infectious diseases, medical ethics, transfusion medicine, epidemiology, biostatistics, and the public considered the evidence and formulated a consensus statement to address the following six predefined questions:

- What is the natural history of hepatitis C?
- What is the most appropriate approach to diagnose and monitor patients?
- What is the most effective therapy for hepatitis C?
- Which patients with hepatitis C should be treated?
- What recommendations to patients can be made to prevent transmission of hepatitis C?
- What are the most important areas for future research?

What is the Natural History of Hepatitis C?

The Virus

The hepatitis C virus is an RNA virus of the Flaviviridae family. Individual isolates consist of closely related yet heterogeneous populations of viral genomes (quasispecies). Probably as a consequence of this genetic diversity, HCV has the ability to escape the host's immune surveillance, leading to a high rate of chronic infection. Comparing the genomic nucleotide sequences from different HCV isolates enables classification of viruses into several genotypes and many more subtypes. The extensive genetic heterogeneity of HCV has important diagnostic and clinical implications, perhaps explaining variations in clinical course, difficulties in vaccine development, and lack of response to therapy.

Clinical Course

Data on the natural history of hepatitis C are limited because the onset of infection is often unrecognized and the early course of the disease is indolent and protracted in many individuals. Prospective cohort studies are few, are typically small, include relatively few subjects whose date of infection can be well documented (e.g., blood transfusion recipients and victims of accidental needle sticks), and have relatively short followup. The natural history of this disease appears to differ according to geography, alcohol use, virus characteristics (e.g., genotype, viral load), coinfection with other viruses, and other unexplained factors.

Acute Infection

After initial exposure, HCV RNA can be detected in blood in 1 to 3 weeks. Within an average of 50 days (range: 15 to 150 days), virtually all patients develop liver cell injury, as shown by elevation of serum alanine aminotransferase (ALT). The majority of patients are asymptomatic and anicteric. Only 25 to 35 percent develop malaise, weakness, or anorexia, and some become icteric. Fulminant liver failure following HCV infection has been reported but is a rare occurrence. Antibodies to HCV (anti-HCV) almost invariably become

detectable during the course of illness. Anti-HCV can be detected in 50 to 70 percent of patients at the onset of symptoms and in approximately 90 percent of patients 3 months after onset of infection. HCV infection is self-limited in only 15 percent of cases. Recovery is characterized by disappearance of HCV RNA from blood and return of liver enzymes to normal.

Chronic Infection

About 85 percent of HCV-infected individuals fail to clear the virus by 6 months and develop chronic hepatitis with persistent, although sometimes intermittent, viremia. This capacity to produce chronic hepatitis is one of the most striking features of HCV infection. The majority of patients with chronic infection have abnormalities in ALT levels that can fluctuate widely. About one-third of patients have persistently normal serum ALT levels. Antibodies to HCV or circulating viral RNA can be demonstrated in virtually all patients.

Chronic hepatitis C is typically an insidious process, progressing, if at all, at a slow rate without symptoms or physical signs in the majority of patients during the first two decades after infection. A small proportion of patients with chronic hepatitis C, perhaps fewer than 20 percent, develop nonspecific symptoms, including mild intermittent fatigue and malaise. Symptoms first appear in many patients with chronic hepatitis C at the time of development of advanced liver disease.

In chronic hepatitis, inflammatory cells infiltrate the portal tracts and may also collect in small clusters in the parenchyma. The latter instance is usually accompanied by focal liver cell necrosis. The margin of the parenchyma and portal tracts may become inflamed, with liver cell necrosis at this site (interface hepatitis). If and when the disease progresses, the inflammation and liver cell death may lead to fibrosis. Mild fibrosis is confined to the portal tracts and immediately adjacent parenchyma. More severe fibrosis leads to bridging between portal tracts and between portal tracts and hepatic veins. Such fibrosis can progress to cirrhosis, defined as a state of diffuse fibrosis in which fibrous septae separate clusters of liver cells into nodules. The extent of fibrosis determines the stage of disease and can be reliably assessed.

Severe fibrosis and necroinflammatory changes predict progression to cirrhosis. Once cirrhosis is established, complications can ensue that are secondary to liver failure and/or to portal hypertension, such as jaundice, ascites, variceal hemorrhage, and encephalopathy. The development of any of these complications marks the transition from a compensated to a decompensated cirrhosis.

The rate of progression is highly variable. Long-term studies suggest that most patients with progressive liver disease who develop cirrhosis have detectable ALT elevations; these can, however, be intermittent. The relationship is inconsistent between ALT levels and disease severity as judged histologically. Although patients with HCV infection and normal ALT levels have been referred to as "healthy" HCV carriers, liver biopsies can show histological evidence of chronic hepatitis in many of these patients.

Cirrhosis of the Liver

Chronic hepatitis C infection leads to cirrhosis in at least 20 percent of patients within two decades of the onset of infection. Cirrhosis and end-stage liver disease may occasionally develop rapidly, especially among patients with concomitant alcohol use.

Hepatocellular Carcinoma

Chronic infection by HCV is associated with an increased risk of liver cancer. The prevailing concept is that hepatocellular carcinoma (HCC) occurs against a background of inflammation and regeneration associated with chronic hepatitis over the course of approximately three or more decades. Most cases of HCV-related HCC occur in the presence of cirrhosis.

The risk that a person with chronic hepatitis C will develop HCC appears to be 1 to 5 percent after 20 years, with striking variations in rates in different geographic areas of the world. Once cirrhosis is established, the rate of development of HCC increases to 1 to 4 percent per year. Among patients with cirrhosis due to hepatitis C, HCC develops more commonly in men than in women and in older than in younger patients.

Extrahepatic Manifestations of HCV

Patients with chronic hepatitis C occasionally present with extrahepatic manifestations or syndromes considered to be of immunologic origin, including arthritis, keratoconjunctivitis sicca, lichen planus, glomerulonephritis, and essential mixed cryoglobulinemia. Cryoglobulins may be detected in the serum of about one-third of patients with HCV, but the clinical features of essential mixed cryoglobulinemia develop in only about 1 to 2 percent of patients. Chronic hepatitis C may be a major underlying cause of porphyria cutanea tarda.

Mortality

After an average followup of 18 years, a prospective study of patients who received blood transfusions showed no difference in overall mortality between HCV-infected cases and noninfected controls. Liver-related mortality, although rare, was twice as high in the cases (3.2 percent vs. 1.5 percent). A recent European study showed that survival among hepatitis C patients with compensated cirrhosis was 91 percent after 5 years and 79 percent after 10 years. Among patients developing decompensated cirrhosis, however, 5-year survival was only 50 percent.

What Is the Most Appropriate Approach to Diagnose and Monitor Patients?

A variety of tests are available for hepatitis C diagnosis. Tests that detect antibody against the virus include the enzyme immunoassays (EIAs), which contain HCV antigens from the core and nonstructural genes, and the recombinant immunoblot assays (RIBAs), which contain the same HCV antigens as EIA in an immunoblot format. In addition, several polymerase chain reaction (PCR)-based assays for HCV RNA have been developed to detect the RNA virus directly. Liver biopsy can determine the extent of liver injury due to HCV. Although some histologic findings are characteristic of HCV infection, such as portal lymphoid aggregates, steatosis, and bile duct injury, these alone are not sufficiently specific to establish a diagnosis of hepatitis C. There are currently no reliable, readily available tests for detection of HCV antigens in the liver.

The EIA tests are reproducible and inexpensive and have been automated. They are suitable for screening low- and high-prevalence populations and as an initial test for patients with clinical liver disease. The RIBA test is most frequently used as a supplemental assay. Qualitative HCV RNA detection by reverse transcription (RT)-PCR is generally accepted as the most sensitive test, and a standardized assay has been developed. However, significant variability of results among laboratories has been reported in proficiency surveys. Clinicians should be aware of the proficiency record of laboratories performing HCV RNA testing to ensure test accuracy for their patients.

Using carefully standardized research PCR tests for HCV RNA as a reference standard, the sensitivity of the second-generation enzyme immunoassay, EIA-2, is 92 to 95 percent. Its specificity has not been precisely established. Studies performed to date indicate that 25 to 60 percent of blood donors with no risk factors for hepatitis C who are positive by the EIA-2 test are also positive by the PCR test for HCV RNA. Of low-risk donors who are both EIA-2 and RIBA-positive, 70 to 75 percent are positive for HCV RNA. Positive predictive

values are much higher in patients with hepatitis C risk factors, elevated ALT levels, or clinical liver disease.

Practitioners frequently encounter patients suspected of having HCV infection. In low-risk populations, such as blood donors who report no risk factors for HCV (e.g., parenteral drug use, history of transfusion, multiple sexual partners), a negative EIA test is sufficient to rule out infection. However, low-risk individuals with positive EIA tests should undergo supplementary RIBA testing. If the RIBA is negative, the anti-HCV EIA result is likely to have been a false positive, and the patient is unlikely to have hepatitis C. If the RIBA is positive, the patient can be assumed to have or to have had hepatitis C. These patients can benefit by testing for HCV RNA by PCR, the result of which will indicate whether the patient has ongoing viremia. A single positive assay for HCV RNA by PCR confirms HCV infection; unfortunately, a single negative assay does not prove that the patient is not viremic or has recovered from hepatitis C. Followup testing for ALT levels and perhaps repeating the HCV RNA in the future may be needed. If the results of the RIBA are "indeterminant," follow-up testing is indicated to demonstrate whether HCV RNA is present. It is hoped that further advances in anti-HCV testing will eventually decrease the percentage of false-positive EIA and indeterminant RIBA results.

Individuals with even mildly elevated ALT levels, with or without risk factors for hepatitis C, should be tested for anti-HCV by EIA and, if positive, the results confirmed by either supplemental RIBA or qualitative HCV RNA by PCR. Obviously anti-HCV testing is very helpful in all patients with clinical liver disease.

In patients presenting with biochemical or clinical evidence of liver disease (e.g., repeatedly elevated ALT levels), a positive EIA test is sufficient to diagnose hepatitis C infection, especially if risk factors are present. A qualitative HCV RNA test can be used for confirmation. If the patient is being considered for antiviral therapy, liver biopsy is of value to assess disease severity.

Testing for serum ALT levels is the most inexpensive and noninvasive means of assessing disease activity. However,

a single determination of ALT levels is not always accurate in reflecting the severity of the underlying liver disease. In most studies, there is only a weak association between ALT levels and severity of the histopathological findings on liver biopsy. Serial determinations of ALT levels over time may provide a better means of assessing liver injury, but the accuracy of this approach has not really been shown. Nevertheless, the resolution of elevated ALT levels with antiviral therapy does appear to be an important indicator of disease response, and serial determinations of ALT levels can be recommended as the general means of monitoring patients with this disease.

Testing for HCV RNA by PCR can be very helpful in initial diagnosis, but repeat testing over time is generally not helpful in management of untreated patients; almost all remain viremic, and a negative result may merely reflect a transient fall of viral titer below the level of detection rather than permanent clearance. On the other hand, repeat testing for HCV RNA during antiviral therapy can be helpful because loss of HCV RNA with treatment is a strong predictor of a sustained beneficial response.

Testing for HCV RNA level (or viral load) by a quantitative assay, either quantitative PCR (qPCR) or the branched DNA signal amplification assay (bDNA), can provide accurate information on viral titer. In many studies, the likelihood of a response to interferon alfa has correlated with a low level of HCV RNA present before treatment. However, there is no level of HCV RNA that absolutely precludes the possibility of a response, and there is little or no correlation between disease severity or disease progression and level or titer of HCV RNA. Furthermore, current assays are not as sensitive as the standard, qualitative PCR test and suffer from lack of standardization. Thus, sequential testing for HCV RNA levels is not clinically helpful in management of patients.

At least 6 genotypes and more than 30 subtypes of HCV RNA have been identified. HCV genotype may be an independent predictor of response to interferon alfa therapy. In many studies, patients with genotypes 2 and 3 are more likely to have a sustained treatment response than those with genotypes 1a or 1b. Methods of genotyping include PCR-based

techniques and, more recently, less expensive serotyping (antibody) assays. However, both genotyping and serotyping should be considered research tools and not part of a diagnostic or therapeutic algorithm in clinical practice.

Liver biopsy is considered the gold standard for assessment of patients with chronic hepatitis. When combined with serial determinations of ALT levels, liver biopsy is very helpful in judging the severity or activity of the liver disease and the stage or degree of fibrosis. Liver biopsy is recommended before treatment to assess the grade and stage of disease and to exclude other forms of liver disease or complications (such as concurrent alcoholic liver disease, medication-induced liver injury, and iron overload). However, liver biopsy is expensive and is associated with some morbidity. Therefore, serial ALT and qualitative HCV RNA testing are recommended for monitoring patients under treatment.

What is the Most Effective Therapy for Hepatitis C?

Although several different forms of interferon have been evaluated in the treatment of patients with chronic hepatitis C, the bulk of available evidence pertains to the alpha interferons (interferon alfa). The efficacy of interferon alfa therapy currently is defined biochemically as normalization of serum ALT and virologically as loss of serum HCV RNA. Therefore, serial ALT testing is recommended for monitoring patients during treatment to document biochemical responses, and testing for HCV RNA by qualitative PCR is recommended at selected time points to document virological responses. Based on these markers, randomized clinical trials have demonstrated that treatment with interferon alfa benefits some patients with chronic hepatitis C. In terms of biochemical response, treatment with interferon alfa at a dosage of 3 million units administered subcutaneously three times weekly for 6 months has produced a biochemical ETR of 40 to 50 percent and a biochemical SR of 15-20 percent In terms of virological response, the 6-month course of treatment has produced an ETR of 30 to 40 percent and an SR of 10 to 20 percent. The biochemical and virological improvement has been accompanied by histological improvement.

Increasing the duration of treatment to 12 months is not associated with higher biochemical or virological ETR, but the biochemical SR is increased to 20 to 30 percent. For patients who do not achieve a biochemical or virological ETR (non-responders), retreatment with a standard dose of interferon alfa is rarely effective. Further therapy with newer interferons and/or higher dosages may achieve a virological SR of only 10 percent. For patients who achieve a biochemical ETR with 6 months of treatment, but who relapse during followup, retreatment for 12 months has been associated with a biochemical ETR rate of 75 to 85 percent and an SR rate of 30 to 40 percent. The benefit of treatment of longer duration is still being evaluated. It should be recognized that although interferon treatment may be associated with favorable effects on biochemical and virological markers, its effects on important clinical outcomes such as quality of life and disease progression remain undetermined.

Three months after beginning an initial course of therapy, patients who are unlikely to respond to that dosage and frequency can be identified by persistent elevation of serum ALT levels and presence of HCV RNA in the serum. In this situation, therapy should be discontinued because the likelihood of future response is extremely low. If either HCV RNA is negative or ALT levels are normal (or both), therapy should be continued for 12 months. Nonresponders should be encouraged to participate in clinical trials directed toward this difficult-to-treat group.

Most of the clinical trials in chronic hepatitis C have evaluated interferon alfa-2b. Other trials have used interferon alfa-2a, interferon alfa-n1, consensus interferon, interferon beta, and interferon alfa-n3. All forms of interferon appear to have similar efficacy in chronic hepatitis C.

Because most patients do not experience sustained response, attempts have been made to identify individuals who are more likely to respond to therapy. The important factors associated with a favorable response to treatment include HCV genotype 2 or 3, low serum HCV RNA level (less than 1,000,000 copies/mL), and absence of cirrhosis.

Flulike symptoms (fever, chills, malaise, headache, arthralgia, myalgia, tachycardia) occur early in the majority of patients who receive interferon but generally diminish with continued therapy. Later side effects include fatigue, alopecia, bone marrow suppression, and neuropsychiatric effects such as apathy, cognitive changes, irritability, and depression. Relapse of drug and/or alcohol abuse may occur. Nocturnal administration of interferon reduces the frequency of side effects, and the flulike syndrome is ameliorated by pretreatment with acetaminophen. A reduction in interferon dosage is required in 10 to 40 percent of patients because of side effects, and treatment must be discontinued in 5 to 10 percent. Higher dosages tend to be associated with higher rates of side effects.

Severe side effects are observed in less than 2 percent of patients. These include autoimmune disease (thyroid disease being most common), depression with suicidal risk, seizure disorder, acute cardiac and renal failure, retinopathy,

interstitial pulmonary fibrosis, hearing impairment, and sepsis. Rare deaths have occurred caused by liver failure or sepsis, principally in patients with cirrhosis.

An important side effect of interferon in hepatitis C is a paradoxical worsening of liver disease with therapy. This exacerbation of hepatitis is probably an autoimmune reaction, and it can be severe. Indeed, fatal occurrences have been reported. Thus, patients with hepatitis C whose serum ALT levels increase on therapy should be followed more carefully, and if levels rise to greater than twice the baseline, interferon should be promptly discontinued.

It is appropriate that a percutaneous liver biopsy be obtained before initiating therapy with interferon to assess the degree of necroinflammatory activity, the extent of fibrosis, and the presence of any other cause of liver injury. Laboratory tests that should be obtained before starting therapy include liver chemistries (serum ALT, bilirubin, albumin, prothrombin time), complete blood count (CBC) with differential and platelet count, antinuclear antibodies, thyroid stimulating hormone, serum HCV RNA, and glucose. Monitoring during therapy should be done at 2- to 4-week intervals with serum ALT and CBC. Both serum ALT and serum HCV RNA testing should be done after 3 months to assess whether the patient is responding to therapy. This should be repeated at the end of therapy to document end-of-treatment response. Follow-up testing, with serum ALT and serum HCV RNA, should be done 6 months after therapy is stopped to determine whether there has been a sustained response. Followup liver biopsy is not necessary.

Disappointing results with interferon have prompted interest in new treatment approaches to chronic hepatitis C. Early work with corticosteroids, ursodiol, and thymosin has produced scant or no evidence of sustained benefit. High concentrations of iron in liver tissue may blunt the response to interferon. This has sparked interest in iron reduction therapy, through phlebotomy or chelation, in an attempt to enhance the response to interferon. Thus far, studies of iron reduction have been inconclusive.

The adjunctive drug of most promise, at present, is ribavirin, an oral antiviral agent that, when used alone, reduces serum ALT levels in approximately 50 percent of patients. However, ribavirin by itself does not lower serum HCV RNA levels, and relapses occur in virtually all patients when therapy is stopped. Of greater promise are recent reports that the combination of interferon alfa and ribavirin leads to sustained virological response rates (40 to 50 percent) higher than for interferon alfa alone in 6-month clinical trials. Ribavirin has not been licensed or approved for use in hepatitis C by the Food and Drug Administration. Large-scale trials of the combination in hepatitis C are now under way. Combination therapy with ribavirin and interferon has also shown promise in the retreatment of those who relapse. Hemolytic anemia has been the major side effect of ribavirin, necessitating a dosage reduction in more than 10 percent of patients.

Which Patients With Hepatitis C Should Be Treated?

All patients with chronic hepatitis C are potential candidates for specific therapy. However, given the current status of therapies for hepatitis C, treatment is clearly recommended only in a selected group of patients. In others, treatment decisions are less clear and should be made on an individual basis or in the context of clinical trials.

Treatment is recommended for the group of patients with chronic hepatitis C who are at the greatest risk for progression to cirrhosis. These patients are characterized by persistently elevated ALT, positive HCV RNA, and a liver biopsy with either portal or bridging fibrosis and at least moderate degrees of inflammation and necrosis.

Indication for therapy is less obvious in other groups of patients. One such group consists of patients with persistent ALT elevations, but with less severe histological changes, that is, no fibrosis and minimal necroinflammatory changes. In these patients, progression to cirrhosis is likely to be slow, if at all; therefore, observation and serial measurements of ALT and liver biopsy every 3 to 5 years are an acceptable alternative to treatment with interferon. Another such group consists of patients with compensated cirrhosis (without jaundice, ascites, variceal hemorrhage, or encephalopathy), in whom current data do not definitively show that interferon therapy will prolong survival or delay development of hepatocellular carcinoma. Similarly, firm recommendations on treatment with interferon cannot be made for patients younger than age 18 or older than age 60 because of incomplete data. In all these groups of patients, treatment decisions should be made jointly between patient and physician, after full discussion of risks and benefits. However, where possible, treatment in these instances should be undertaken in the context of clinical trials, so that data become available for future decisionmaking.

Patients with decompensated cirrhosis should not be treated with currently available therapy for hepatitis C and should be considered for liver transplantation. Therapeutic trials for hepatitis C in these patients should be performed only in the

setting of clinical trials carried out in collaboration with liver transplant centers.

Data suggest a benefit from interferon treatment with higher clearance of HCV RNA in patients with acute hepatitis C. In light of these findings, interferon treatment of patients with acute hepatitis C could be recommended.

Current studies suggest that treatment of patients with persistently normal ALT is not beneficial and may actually induce liver enzyme abnormalities. Therefore, these patients should not receive therapy outside of placebo-controlled clinical trials.

Nonspecific symptoms such as fatigue are difficult to interpret and should not influence treatment decisions. However, patients with clinical evidence of essential mixed cryoglobulinemia could benefit from long-term therapy with interferon.

Because severity of disease or progression to cirrhosis has not been conclusively related to the mode of acquisition of hepatitis C or to particular risk groups, therapy should not be denied on the basis of these factors. However, treatment of patients who are drinking significant amounts of alcohol or who are actively using illicit drugs should be delayed until these habits are discontinued for at least 6 months. Such patients are at risk for the potential toxic effects of alcohol and other drugs and also present problems with compliance. Treatment for addiction should be provided before treatment for hepatitis C.

Patients with chronic hepatitis C and concurrent HIV infection may have an accelerated course of disease. Therefore, patients who have stable HIV infection with good clinical and functional status should be considered for treatment, according to guidelines outlined in this statement.

Even though high HCV RNA levels or genotype 1 predict a less favorable response to therapy, treatment should not be withheld on the basis of these parameters.

Contraindications to treatment with interferon that must be carefully considered are history of major depressive illness, cytopenias, hyperthyroidism, renal transplant, and convincing evidence of autoimmune disease.

What Recommendations Can Be Made to Patients To Prevent Transmission of Hepatitis C?

The large reservoir of individuals infected with HCV globally provides a source of transmission to others at risk. Before the identification of HCV, the majority of non-A, non-B hepatitis cases were associated with blood transfusion, injection drug use, health care, employment, or sexual or household exposure to a contact with hepatitis. HCV is now rarely transmitted by transfusion because of screening tests that exclude infectious donors.

Direct percutaneous exposure is the most efficient method for transmitting HCV. In drug users, HCV infection is acquired rapidly after beginning injection drug use, with 50 to 80 percent of new users becoming positive for antibody to HCV within 6 to 12 months. Injection drug use accounts for half of all new infections annually and perhaps greater than 50 percent of chronic infections. In addition, it is thought that the majority of the rest of the cases can be explained by transfusion before 1990, occupational exposures to blood, hemodialysis, high-risk sexual activity (multiple partners, history of sexually transmitted diseases), and noninjection illegal drug use (intranasal cocaine). Percutaneous exposures such as body piercing and tattooing are potential sources of transmission if contaminated equipment or supplies are used, although their role in transmission of HCV in the United States has not been confirmed. It is now considered that the route of transmission is unknown in less than 10 percent of newly acquired cases of hepatitis C.

Data regarding transmissibility by sexual contact have been conflicting. Based on studies in sexually transmitted disease clinics, sexual transmission appears to occur; however, even with multiple sexual partners the risk is low. The risk appears to be increased by coinfection with HIV or other sexually transmitted diseases. Although transmission in long-term monogamous relationships may occur, the risk is thought to be minimal.

There is some evidence for occupational and nosocomial transmission of HCV infection. Health care workers have a higher prevalence than the general population, although many may have acquired it from other sources. However, inadvertent needle stick injuries and lack of application of universal precautions may be contributing factors. The risk of infection from needle sticks in hepatitis C is intermediate between that of HIV and hepatitis B. HCV transmission between patients in dialysis centers may be related to poor infection control practices. Although transmission from health care workers to patients has been documented, such transmission is thought to be rare.

Perinatal transmission between mother and baby has been documented, although the risk is estimated at no more than 6 percent. The risk is increased if the mother is coinfected with HIV. Although data are limited, there is no evidence that breast-feeding transmits HCV from mother to baby.

What Are the Most Important Areas for Future Research?

Continued monitoring of the epidemiology of acute and chronic hepatitis C is necessary. Additional studies of the specific mode of transmission in minority groups, low socioeconomic groups, institutionalized individuals, and injection and intranasal drug users are needed, as well as more information on sexual, household, occupational, nosocomial, and perinatal transmission.

Large-scale, long-term studies are needed to better define the natural history of hepatitis C and especially to identify factors associated with disease progression to cirrhosis. Studies of the natural history are needed in special groups, such as minorities, children, those older than 60, HCV-infected patients with normal ALT, HCV-infected patients coinfected with HIV, and injection drug users. Information is also needed about the role of ultrasound and alpha fetoprotein monitoring for early detection of hepatocellular carcinoma in patients with chronic hepatitis C.

Studies are needed on the recovery from and persistence of viral infection as well as the pathogenesis and mechanism of liver cell injury by HCV. Is damage caused by cytopathic effects of the virus on the liver cell, or is it immunologically mediated? What is the mechanism of hepatic fibrosis? Can fibrosis be separated from inflammation/necrosis of the liver? Such studies would be greatly facilitated by development of suitable animal and cell culture models. The mechanism of development of hepatocellular carcinoma in patients with hepatitis C needs elucidation.

Given the large number of persons who are already infected with HCV, there is an urgent need for effective antiviral therapeutics capable of inhibiting virus replication and stopping or delaying the progression of liver disease. A major bottleneck to the drug discovery process is the absence of a readily available cell culture system that is fully permissive for viral replication. Thus, development of such systems should be a high priority. An improved understanding of the molecular

virology of HCV is also critically important to antiviral drug development. These studies should include the development of infectious molecular clones, which would allow analyses of structure-function relations among HCV nonstructural proteins that participate in the viral replication cycle.

Alcohol ingestion clearly worsens the course of hepatitis C, but the reasons for this interaction are unknown. Studies of the interaction between HCV and obesity, diabetes mellitus, iron, and medications are also needed.

Unresolved questions remain regarding the diagnostic tests for hepatitis C. What is the prevalence of significant liver disease among RIBA-positive, HCV RNA-negative individuals? What should be the gold standard for HCV RNA assays? What is the frequency of intermittent viremia in untreated patients? What are the criteria for selecting patients for, or withdrawing patients from, treatment? How can the reliability of HCV RNA tests be improved? How can the dynamic range and intra-assay variability of the HCV RNA test be improved?

Future clinical trials should expand the range of outcomes studied to include quality of life from the patient's point of view, as well as costs and survival. In addition, those trials should include minorities, patients older than age 60, patients younger than age 18, HIV-coinfected patients, and liver transplant patients. We need to identify effective, nontoxic therapeutic agents. Clinical trials are also needed to identify optimal treatment regimens for those who do not respond to interferon therapy or who relapse following interferon therapy. Studies are needed to identify and test prospectively the factors that predict response to therapy. In addition, studies are needed of possible drug interactions, especially between the antiretroviral drugs used to treat HIV infection and those drugs used to treat hepatitis C.

Although continued education of risk groups and screening of blood, organs, tissue, and semen remain vitally important, the key to prevention is development of an effective and safe vaccine for hepatitis C. This will require a better understanding of the molecular determinants of both cellular and humoral

immunity to HCV, the nature of antigenic variation as related to viral quasispecies diversity, and the mechanism(s) by which HCV regularly eludes the host immune system and establishes persistent infection.

Strategies should be developed to educate at-risk groups concerning transmission of disease, as well as provide access to diagnosis and treatment. It would be helpful also to evaluate the role of intranasal cocaine use as a possible route of infection.

Conclusions and Recommendations

Individuals who have a history of transfusions of blood or blood products before 1990, who are on chronic hemodialysis, who have a history of injection drug use, who have had multiple sexual partners, who are the spouses or close household contacts of hepatitis C patients, and who share instruments for intranasal cocaine use should be tested for hepatitis C.

Hepatitis C is a common infection with a variable course that can lead to chronic hepatitis, cirrhosis, liver failure, and hepatocellular carcinoma. The course of illness may be adversely affected by various factors, especially alcohol consumption. Therefore, more than one drink per day is strongly discouraged in patients with hepatitis C, and abstinence from alcohol is recommended. Those addicted to alcohol or other drugs should be helped to obtain treatment for their addiction so that they might qualify for anti-HCV therapy.

An EIA test for anti-HCV should be the initial test for diagnosis of hepatitis C. In low-risk populations, a supplemental RIBA test and/or a qualitative PCR test for HCV RNA should be performed in those whose EIA test is positive. In patients with clinical findings of liver disease, HCV RNA by PCR can be used for confirmation.

Because of assay variability, qualitative and quantitative PCR testing for HCV RNA must be interpreted cautiously. Rigorous proficiency testing is recommended for clinical laboratories performing this assay. The branched DNA signal amplification assay for viral level has been standardized but may fail to detect low titers of HCV RNA. Sequential measurement of HCV RNA levels (viral load) has not, to date, proven useful in managing patients with hepatitis C.

Liver biopsy is indicated when histologic findings will assist decisionmaking regarding patient management. In patients who are not treated with antiviral therapy initially, liver biopsy can be considered to assess disease progression.

HCV genotyping and tests for HCV RNA levels (viral load) may provide useful prognostic information, especially regarding response to therapy, but at present must be considered research tools.

Currently available therapy for chronic hepatitis C is indicated for patients who have persistently abnormal ALT (greater than 6 months), a positive HCV RNA, and liver biopsy demonstrating either portal or bridging fibrosis and at least moderate degrees of inflammation and necrosis. Patients with milder histological disease, compensated cirrhosis, or who are younger than age 18 or older than 60 should be managed on an individual basis or in the context of clinical trials. Patients with decompensated cirrhosis should not be treated with interferon but should be considered for liver transplantation. Patients with persistently normal ALT and minimal histologic abnormalities should not be treated outside clinical trials. Contraindications to treatment of patients with interferon that must be considered are a history of major depressive illness, cytopenia, active alcohol use or illicit drug use, hyperthyroidism, renal transplantation, or autoimmune disease. Therapy should not be limited by mode of acquisition, risk group, HIV status, HCV RNA level, or genotype.

Because 12-month regimens with interferon are more successful in achieving sustained responses, initial therapy with interferon alfa (or its equivalent) should be 3 million units three times weekly subcutaneously for 12 months.

Nonresponders to interferon therapy can be identified early by assessing the serum ALT level and presence of serum HCV RNA after 3 months of therapy. If the ALT level remains abnormal and the serum HCV RNA remains detectable, interferon therapy should be stopped because further treatment is unlikely to produce a response. Nonresponders should not be retreated with the same regimen but should be considered for combination therapy or enrollment in investigational protocols using different dosages or agents.

Patients who have an end-of-treatment response to a 6-month course of interferon alfa but then relapse should receive retreatment with a 12-month course of interferon alfa or be considered for combination therapy with interferon plus ribavirin or other regimens, preferably in a clinical trial.

Hepatitis A and B vaccination is recommended for all HCV-positive patients.

Patient support groups should be encouraged, especially for those undergoing therapy, those who fail therapy, and those recovering from addiction.

The following recommendations are made to avoid transmission of hepatitis C:

1. In health care settings, adherence to universal (standard) precautions for the protection of medical personnel and patients is essential.

2. HCV-positive individuals should refrain from donating blood, organs, tissues, or semen. In some situations, the use of organs and tissues from HCV-positive individuals may be considered. For example, in emergency situations the use of a donor organ in which the HCV status is either positive or unknown may be considered in a HCV-negative recipient after full disclosure and informed consent. Strategies should be developed to identify prospective blood donors with any prior history of injection drug use. Such individuals must be deterred from donating blood.

3. Safer sexual practices should be strongly encouraged in persons with multiple sexual partners, including the use of latex condoms. In monogamous long-term relationships, transmission is rare. Although HCV-positive individuals and their partners should be informed of the potential for transmission, there are insufficient data to recommend changes in current sexual practice in persons with a steady partner. It is recommended that sexual partners of infected patients should be tested for antibody to HCV.

4. In households with an HCV-positive member, sharing razors and toothbrushes should be avoided. Covering open wounds is recommended. Injection needles should be carefully disposed of using universal precaution techniques. It is not necessary to avoid close contact with family members or to avoid sharing meals or utensils. There is no evidence to justify exclusion of HCV-positive children or adults from participation in social, educational, and employment activities.

5. Pregnancy is not contraindicated in HCV-infected individuals. Perinatal transmission from mother to baby occurs in less than 6 percent of instances. There is no evidence that breast-feeding transmits HCV from mother to baby; therefore, it is considered safe. Babies born to HCV-positive mothers should be tested for anti-HCV at 1 year.

6. Needle exchange and other safer injection drug use programs may be of benefit in reducing parenterally transmitted diseases. Expansion of such programs should be considered in an effort to reduce the rate of transmission of hepatitis C.

7. It is important that clear and evidenced-based information be provided to both patients and physicians regarding the natural history, means of prevention, management, and therapy of hepatitis C.

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Management of Hepatitis C

A Continuing Medical Education Activity Sponsored by the National Institutes of Health

OBJECTIVE

The objective of this NIH Consensus Statement is to inform the biomedical research and clinical practice communities of the results of the NIH Consensus Development Conference on Management of Hepatitis C. The statement provides state-of-the-art information regarding natural history, diagnosis, treatment, management, and prevention of hepatitis C and presents the conclusions and recommendations of the consensus panel regarding these issues. In addition, the statement identifies those areas of study that deserve further investigation. On completing this educational activity, the reader should possess a clear working clinical knowledge of the state of the art regarding this topic.

ACCREDITATION

The NIH/FAES is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians.

The NIH/FAES designates this continuing medical education activity for 1 credit hour in Category I of the Physician's Recognition Award of the American Medical Association. Each physician should claim only those hours of credit that he or she actually spent in the educational activity.

EXPIRATION

This form must be completed and **postmarked by October 31, 1998** for eligibility to receive continuing medical education credit for this continuing medical education activity. The expiration date for this test may be extended beyond October 31, 1998. Beginning November 1, 1998, please check the NIH Consensus Development Program Web site (http://consensus.nih.gov) or call the NIH Office of Medical Applications of Research at (301) 496-1144 for information regarding an extended expiration date for this continuing medical education activity.

INSTRUCTIONS

The consensus statement contains the correct answers to the following 15 questions. Select your answer(s) to each question and write the corresponding letter(s) in the answer space provided. Mail the completed test by the expiration date shown above to the address at the end of this test. You will receive notification of your test results within 2 to 3 weeks. If you have successfully completed the test (11 or more correct answers), you will receive a certificate for 1 hour of CME credit along with your test results. Photocopies of this form are acceptable. There is no fee for participating in this continuing education activity.

National Institutes Of Health
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a. is most often caused by transfusions of blood or blood products
b. accounts for at least 50 percent of cases of acute hepatitis in the United States
c. frequently is symptomatic
d. none of the above

ANSWER(S): _____

2. **Risk factors for acquiring hepatitis C include:** *(You must indicate all that are true.)*
   a. injection drug use
   b. sexual promiscuity
   c. intranasal cocaine use
   d. none of the above

   ANSWER(S): _____

3. **In the course of acute hepatitis C virus (HCV) infection, the first abnormality to occur is:**
   a. anti-HCV reactivity in serum
   b. HCV RNA reactivity in serum
   c. symptoms of hepatitis such as fatigue and nausea
   d. elevations in serum alanine aminotransferase (ALT) levels

   ANSWER: _____

4. **Chronic hepatitis C:** *(You must indicate all that are true.)*
   a. is usually asymptomatic
   b. leads to cirrhosis in most cases
   c. is a contraindication to liver transplantation
   d. none of the above

   ANSWER(S): _____

5. **Extrahepatic manifestations of hepatitis C include:** *(You must indicate all that are true.)*
   a. cryoglobulinemia
   b. glomerulonephritis
   c. seronegative arthritis
   d. none of the above

   ANSWER(S): _____

6. **The best test for screening for hepatitis C is:**
   a. qualitative tests for HCV RNA (PCR)
   b. quantitative tests for HCV RNA (viral load)
   c. anti-HCV by enzyme immunoassay (EIA)
   d. anti-HCV by recombinant immunoblot (RIBA)
   e. immunostaining for HCV antigen in liver

   ANSWER: _____

7. **Liver biopsy is useful in patients with chronic hepatitis C:** *(You must indicate all that are true.)*
   a. in establishing the diagnosis of hepatitis C
   b. in assessing the activity of the disease
   c. in assessing whether cirrhosis is present
   d. in assessing the need for therapy
   e. in proving that a beneficial response to interferon therapy has occurred

   ANSWER(S): _____

8. **After donating blood, a 28-year-old woman is told that she tested positive for anti-HCV. She has no symptoms and no previous history of hepatitis or known risk factors. Which of the following would be appropriate in the initial evaluation for hepatitis C?** *(You must indicate all that are true.)*

ANSWER(S): _____

9. The following patients all have chronic hepatitis C with anti-HCV and HCV RNA in serum and a liver biopsy showing chronic hepatitis. All have been tested for serum alanine aminotransferase (ALT) levels, normal being <40 U/L. Which of the following individuals would be reasonable candidates for alpha interferon therapy? *(You must indicate all that are true.)*
   a. 60-year-old renal transplant patient with abnormal ALT levels (105 U/L)
   b. 35-year-old woman with normal ALT levels (24 U/L)
   c. 50-year-old man with abnormal ALT levels (150 U/L) and HCV genotype 1b
   d. 40-year-old woman with cryoglobulinemia and minimally abnormal ALT levels (52 U/L)
   e. 25-year-old injection drug user who has been in rehabilitation for 1 month and has abnormal ALT levels (225 U/L)

   ANSWER(S): _____

10. The currently recommended therapy of chronic hepatitis C is use of alpha interferon. Recommended duration of therapy is:
   a. 6 months b. 12 months c. 18 months

   ANSWER(S): _____

11. The recommended dose of alpha interferon for chronic hepatitis C is:
   a. 3 million units daily
   b. 5 million units daily
   c. 3 million units three times weekly
   d. 5 million units three times weekly
   e. 10 million units three times weekly

   ANSWER(S): _____

12. A 48-year-old man with chronic hepatitis C (anti-HCV and HCV RNA in serum, liver biopsy showing moderate degrees of fibrosis and inflammation, and alanine amino-transferase levels of 100-200 U/L) is started on alpha interferon therapy. After 3 months blood testing shows that his serum alanine aminotransferase is 72 U/L (normal <41 U/L), and he is still positive for HCV RNA in serum. What would you recommend?
   a. increase the dose and continue therapy for 3 more months
   b. increase the dose and continue therapy for 9 more months
   c. continue current regimen of therapy and reassess in 3 more months
   d. perform a liver biopsy and if improvement is seen, continue therapy
   e. stop therapy

   ANSWER: _____

13. During alpha interferon therapy, blood tests that are helpful in monitoring patients with hepatitis C include: *(You must indicate all that are true.)*
   a. serum aminotransferases
   b. thyroid function tests
   c. HCV RNA levels (quantitative testing)
   d. HCV RNA presence (qualitative testing)
   e. HCV genotype

   ANSWER(S): _____

[redacted]

ANSWER: _____

15. Recommendations to patients with chronic hepatitis C should include:
(You must indicate all that are true.)

a. limit intake of alcoholic beverages to less than one drink per day
b. have sexual partners checked for anti-HCV
c. avoid serving or preparing food for others
d. receive hepatitis A vaccination
e. receive hepatitis B vaccination

ANSWER(S): _____

[redacted]

Was the objective of this continuing education activity clearly stated?

a. [redacted] c. somewhat e. completely
b. very little d. considerably

ANSWER: _____

Did the activity planners provide the necessary information to meet the stated goals and objectives?

a. not at all c. somewhat e. completely
b. very little d. considerably

ANSWER: _____

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